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HYDROXYLATION PROCESS FOR AROMATIC COMPOUNDS CONTAINING A DIOXA-HETEROCYCLIC  
SYSTEM

The present invention relates to a hydroxylation process of aromatic compounds containing a heterocyclic system.

More specifically, the present invention relates to a process for the hydroxylation of 1,3-benzodioxoles.

Even more specifically, the present invention relates to a process for the oxidation of 1,3-benzodioxole (MDB) to give 5-hydroxy-1,3-benzodioxole (5-hydroxy-MDB).

Processes are known in literature, for the oxidation of aromatic compounds containing a heterocyclic system, such as benzodioxoles, which give, for example, products such as 5-hydroxy-MDB, a product which is used in agriculture and in the pharmaceutical and cosmetic industry and as an intermediate for organic syntheses.

English patent GB 2,323,843, for example, describes a process for the preparation of 5-hydroxy-MDB which consists in the oxidation of heliotropin with hydrogen peroxide ( $H_2O_2$ ) in the presence of formic acid, according to the

Baeyer Villiger reaction. This process, however, has the disadvantage of using a costly raw material as it is of a natural origin and is not easily available due to the fact that heliotropin is extracted from the sassafras plant currently protected by laws for the protection of the environment.

Another known process for producing 5-hydroxy-MDB is described in Japanese patent application 56-834865 of 1979. This process starts from MDB with the formation of the acetyl derivative, methylenedioxyacetophenone, followed by Baeyer Villiger oxidation using peracids. This method, currently in use, has the disadvantage of creating problems of an environmental nature due to the use of Friedel Kraft catalysts, the presence of methylenedioxyacetophenone and the use of dangerous oxidants, such as peracetic acid, in the oxidation phase of the corresponding acetophenone. As a whole, this synthesis method is characterized by two distinct phases, each of which is marked by heavy reaction conditions due to the use of particularly polluting catalysts and particularly dangerous reagents which are not easy to handle.

Another process described in Japanese patent application 63-45756 of 1993, starts from the derivative 5-bromo-1,3-benzodioxole followed by transformation into a borane derivative, by means of the Grignard reaction, and subse-

quent oxidation of the borane derivative with  $H_2O_2$ . This process is extremely lengthy, involves the use of various reagents which are not easy to handle on an industrial scale, such as the Grignard reactive intermediate and metallic magnesium, and the use of the borane agent which must then be oxidized in a second phase to the corresponding 5-hydroxy-MDB. The various passages of this process are onerous from an economical point of view due to the cost of the various reagents and waste load to be subjected to special disposal.

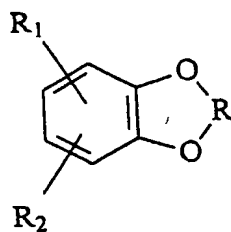
Another process, described in Japanese patent application 52-13384 of 1976, comprises the use of 1,2,4-triphenol as raw material and its subsequent cyclization with methylene chloride in a solvent medium, such as dimethylsulfoxide or dimethylformamide to obtain 5-hydroxy-MDB. This process has the disadvantage of the use of a raw material which is difficult to obtain and the drawback of providing very low reaction yields in the cyclization reaction, as the presence in the phenolic raw material of three equivalent hydroxyl groups leads to the formation of intermolecular methylene bridges in the reaction with the methylene chloride reagent. These by-products depress the yields, make it difficult to recover the desired product and must be sent for special combustion for their disposal.

In conclusion, none of the known processes for the

production of 5-hydroxy-MDB has characteristics which make it interesting from an industrial point of view. These processes are, in fact, jeopardized by the use of costly raw materials, when they are not easily available, and also  
5 by the use of reagents which are difficult to handle or dangerous and in any case characterized by a heavy environmental impact.

The Applicant has now found that it is possible to overcome all the drawbacks of the processes of the known  
10 art for the oxidation of aromatic compounds containing a heterocyclic system, such as benzodioxoles, by means of a direct hydroxylation process of the substrate in the presence of a heterogeneous zeolitic catalyst and hydrogen peroxide.

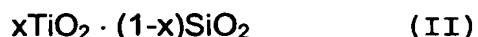
15 An object of the present invention therefore relates to a process for the hydroxylation of aromatic compounds containing a heterocyclic system having general formula (I):



(I)

wherein R represents a C<sub>1</sub>-C<sub>4</sub> (iso)alkylene radical, whereas R<sub>1</sub> and R<sub>2</sub>, the same or different, represent a hydrogen atom  
25 or a CH<sub>3</sub> radical or a halogen, or a C<sub>1</sub>-C<sub>2</sub> alkoxy, which

comprises directly hydroxylating said compounds having general formula (I) with  $H_2O_2$  in the presence of a zeolitic catalyst having general formula (II):



5 wherein  $x$  is a number ranging from 0.0001 to 0.04, preferably from 0.01 to 0.025.

The zeolitic catalyst is known in literature as titanium-silicalite TS-1 and, more specifically, its preparation is described in U.S. patent 4,410,501 and in European  
10 patent 200,260. In the present invention the titanium-silicalite catalyst is used with a particle size ranging from 1 to 1000  $\mu m$ , preferably from 5 to 100  $\mu m$  or in the form of pellets.

According to the present invention, a substrate which  
15 is particularly suitable for being directly hydroxylated is that in which  $R$  is a methylene radical, whereas  $R_1$  and  $R_2$  are two hydrogen atoms. This product is 1,3-benzodioxole (MDB) and can be oxidized in position 5 to form 5-hydroxy-MDB.

20 The hydroxylation reaction can be effected in the presence of one or more solvents or directly in mass, by feeding  $H_2O_2$ , optionally diluted with  $H_2O$ , to a suspension of titanium-silicalite in the substrate, for example MDB, used in a large excess.

25 Solvents which can be used are:

- products belonging to the group of aliphatic alcohols, in particular C<sub>1</sub>-C<sub>10</sub> linear, branched or cyclic alcohols;
- linear, branched or cyclic aliphatic ketones, with a number of carbon atoms ranging from 3 to 12;
- linear, branched or cyclic saturated aliphatic hydrocarbons with a number of carbon atoms ranging from 5 to 12;
- esters selected from dialkyl carbonates wherein the alkyl group contains from 1 to 4 carbon atoms, and esters of carboxylic acid having the formula CH<sub>3</sub>-COO-R' wherein R' represents a C<sub>1</sub>-C<sub>4</sub> radical;
- linear, branched or cyclic aliphatic ethers, with a number of carbon atoms ranging from 3 to 12;
- aliphatic nitriles having the formula R"-CN, wherein R" represents a C<sub>1</sub>-C<sub>4</sub> alkyl radical.

The heterogeneous titanium-silicalite catalyst, known in literature also as TS-1, can be used in batch reactions, in concentrations, with respect to the substrate, varying from 1 to 50% by weight, preferably from 5 to 30%. In this case, the hydrogen peroxide is fed onto a suspension of the TS-1 catalyst in the substrate or onto a suspension consisting of the TS-1 catalyst and a mixture of the substrate with a solvent possibly containing water.

Alternatively, the reaction can also be conveniently

carried out in continuous by feeding hydrogen peroxide and the substrate on a layer of TS-1 catalyst or, preferably, by passing the reagents through a fixed bed of TS-1 catalyst in the form of pellets.

5       The hydrogen peroxide ( $\text{H}_2\text{O}_2$ ) reagent can be used with the concentrations of commercial products, for example with concentrations in hydrogen peroxide ranging from 10 to 60% by weight, but can be further diluted to concentrations lower than 10%. In order to obtain high reaction yields,  
10       the molar ratio  $\text{H}_2\text{O}_2$ /substrate can vary from 0.01 to 0.5, preferably from 0.1 to 0.3. The reaction can be carried out at a temperature ranging from 10 to 100°C, preferably from 40 to 80°C.

      The process, object of the present invention, allows  
15       conversion selectivities of the substrate to hydroxylated product to be obtained, in particular of the MDB substrate to 5-hydroxy-MDB, of up to 80% and with conversions up to 30%. The excess substrate which has not reacted and the TS-1 catalyst can be separated from the reaction mixture and  
20       recycled for the subsequent syntheses.

      Some illustrative but non-limiting examples are provided for a better understanding of the present invention and for its embodiment.

#### EXAMPLE 1

25       30 g of TS-1 catalyst, 150 g of methylisobutylketone,

150 g of acetone and 150 g (1.23 moles) of MDB, are charged into a reactor equipped with a stirrer, thermometer, condenser and heating/cooling jacket. The resulting suspension is heated to 60°C, maintaining the mass under stirring. 84 g of H<sub>2</sub>O<sub>2</sub> at 10% (0.25 moles) are then fed in about 4 hours, the temperature of the suspension being maintained at 60°C. The suspension is left under stirring at 60°C for an hour and the organic phase is subsequently analyzed after separation from the TS-1 catalyst.

10 The following results are obtained from GLC analysis of the organic phase: MDB conversion = 15%; selectivity to 5-hydroxy-MDB = 62%.

#### EXAMPLE 2

The same procedure is used as in Example 1 except that 15 only 300 g of acetone are charged instead of the acetone/methylisobutylketone mixture.

The following results are obtained from GLC analysis of the organic phase: MDB conversion = 12%; selectivity to 5-hydroxy-MDB = 58%.

#### 20 EXAMPLE 3

The same procedure is used as in Example 1, except that 70 g of H<sub>2</sub>O are charged instead of the mixture of solvents and 28 g of H<sub>2</sub>O<sub>2</sub> at 30% (0.25 moles), are dosed.

The following results are obtained from GLC analysis 25 of the organic phase: MDB conversion = 10%; selectivity to



5-hydroxy-MDB = 25%.

EXAMPLE 4

The same procedure is used as in Example 1, except that 33 g of n-hexane are charged instead of acetone.

5 The following results are obtained from GLC analysis of the organic phase: MDB conversion = 10%; selectivity to 5-hydroxy-MDB = 70%.

EXAMPLE 5

The same procedure is used as in Example 1, except  
10 that 150 g of dimethyl carbonate are charged instead of the acetone/methylisobutylketone mixture.

The following results are obtained from GLC analysis of the organic phase: MDB conversion = 13%; selectivity to 5-hydroxy-MDB = 52%.

15 EXAMPLE 6

The same procedure is used as in Example 1, except that 150 g of acetonitrile are charged instead of the acetone/methylisobutylketone mixture.

The following results are obtained from GLC analysis  
20 of the organic phase: MDB conversion = 10%; selectivity to 5-hydroxy-MDB = 45%.

EXAMPLE 7

The same procedure is used as in Example 1, except that 300 g of terbutanol are charged instead of the acetone/methylisobutylketone mixture.  
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The following results are obtained from GLC analysis of the organic phase: MDB conversion = 15%; selectivity to 5-hydroxy-MDB = 48%.

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